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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Applicant	:	Hiles, et al.
Serial No.	:	09/325,095
Filed	:	June 3, 1999
For	:	METHODS FOR DETERMINING EXPRESSION OF A P13 KINASE GENE
Art Unit	:	1645
Examiner	:	J. Hines

December 22, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
MS: Appeal Brief Patents

BRIEF ON APPEAL
(37 CFR §1.192)

Pursuant to 37 C.F.R. §1.192, Applicants appeal from the rejection dated January 27, 2004 and the Advisory Action dated November 12, 2004.

Applicants claims have been rejected more than twice, so appeal is proper.

Pursuant to 37 C.F.R. § 1.192, this Brief on Appeal is filed in triplicate and the fee required by 37 C.F.R. § 1.17(c) accompanies this Brief. A petition for a three month extension of time is also enclosed. In the event any additional fees are due, authorization is hereby given to charge deposit account no. 50-0624.

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I REAL PARTY IN INTEREST

The Real Party in Interest is Ludwig Institute for Cancer Research, the Assignee of the subject application.

II RELATED APPEALS AND INTERFERENCES

To the best of the knowledge of appellants and appellants' legal representative, there are no pending appeals or interferences which will directly affect or be directly affected by this appeal.

III STATUS OF CLAIMS

Claims 51-58, 60 and 61 are pending and have been rejected. A copy of pending claims 51-58, 60 and 61 is appended hereto.

Claims 1-50 and 59 have been canceled.

IV STATUS OF AMENDMENTS

All amendments have been entered. None are currently pending.

V SUMMARY OF THE INVENTION

The invention, which is the subject matter of the claims on appeal, relates to a method for determining expression of a gene which encodes a human polypeptide that has phosphoinositide (hereinafter "PI") 3 kinase activity and a molecular weight of about 110kD. PI3 kinase activity has been shown to affect signaling related to events such as cell growth, differentiation, and survival, and therefore is of great interest for diagnostic and therapeutic purposes. *See e.g.*, page 1, line 34 – page 2, line 2 and page 3, lines 29 – 35.

The claimed method involves contacting a sample with a nucleic acid molecule which hybridizes specifically to a transcript of a gene which encodes a human polypeptide that has PI3 kinase activity at specified hybridization and washing conditions, and determining expression of the gene by determining hybridization.

The specification describes mRNA isolation and cDNA cloning of a gene which encodes a polypeptide that has PI3 kinase activity and a molecular weight of about 110kD. It further describes several hybridization assays.

In a related application which issued as U.S. Patent No. 5,846,824, Applicants claimed specific isolated nucleic acid molecules which encode the catalytic 110kD subunit of PI3 kinase. In a second related application which issued as U.S. Patent No. 6,274,327, Applicants claimed a method for making an antibody which specifically binds to a polypeptide which has PI3 kinase activity and a molecular weight of about 110 kD.

VI SUMMARY OF ISSUES

A. Did the Examiner err in rejecting claims 51-58 and 60-61 under 35 U.S.C § 112, first paragraph, for lack of sufficient written description?

B. Did the Examiner err in rejecting claims 51-58 and 60-61 under 35 U.S.C. § 112, first paragraph, as containing new matter?

C. Did the Examiner err in rejecting claims 51-58 and 60-61 under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps?

D. Did the Examiner err in rejecting claims 51-58 and 60-61 under 35 U.S.C. § 112, second paragraph, as being indefinite?

It is Appellants' contention that the Examiner erred in making all of the above rejections.

VII GROUPING OF CLAIMS

The claims rise or fall together.

VIII ARGUMENT

A. The Rejection of Claims 51-58 and 60-61 for Failing to Satisfy the Written Description Requirement of 35 U.S.C. § 112, First Paragraph, is Erroneous, and Should be Reversed

The written description requirement is contained in 35 U.S.C. § 112, which states, in relevant part:

> "The specification shall contain a written description of the invention, and of the manner and process of using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Whether or not a claimed invention complies with the written description requirement is a fact based inquiry. *See, e.g.*, University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 927 (Fed. Cir. 2004); Enzo Biochem Inc. v. Gen-Probe Inc., 63 U.S.P.Q.2d 609, 612 (Fed. Cir. 2002); Vas-Cath Inc. v. Mahurkar, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991). In order to meet the adequate written description requirement, the applicant does not have to utilize any particular form of disclosure to describe the subject matter claimed, but "the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." In re Gosteli, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989). Put another way, "the applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." Vas-Cath, supra.

The specification, as originally filed, clearly conveys Applicants' invention and the claimed subject matter. For example, pages 40. line 8 – page 41, line 35 of the specification detail three different hybridization techniques (Southern Transfer Hybridization, Northern Transfer Hybridization and PCR Assays). Additional hybridization analyses are detailed on page 46, lines 10 – page 47, line 12 and page 52, lines 18 – page 53, line 24.

The Examiner's first reason for rejecting claims 51-58, and 60-61, as allegedly failing to satisfy the written description requirement is that

> "The specification describes the hybridization method as a separate method from the PCR method, therefore, there is no written description of this entire method as being capable of determining expression of the gene."

See Office Action dated January 27, 2004, page 3. As discussed in Applicants' April 22, 2004 response, PCR is a type of hybridization method, not a separate method as the Examiner maintains. Furthermore, numerous hybridization assays other than PCR are described in the specification. *See, e.g.*, pages 40-41. Therefore, this portion of the rejection is believed to be improper. It is noted that the Examiner does not reiterate this argument in the Advisory Action.

The crux of the Examiner's written description rejection, however, appears to be the argument that hybridization may determine presence of a gene, but does not determine gene expression. *See* Office Action dated January 27, 2004, page 3, line 20 – page 4, line 2. The Examiner maintains that there is no support in the specification for determining gene expression from hybridization. The Examiner also states in the Advisory Action,

> "There is no scientific correlation supported by the specification that if hybridization occurs, gene expression will occur. The monitoring for protein expression of transcripts can be achieved using techniques such as immunological techniques, pulse-chase labelling, immunoprecipitation, epitope tagging, immunohistochemistry and surrogate reporter protein detection. However the specification fails to describe methods for determining gene expression."

Thus, the Examiner appears to assume that if there is gene expression, there must also be protein expression, and since Applicants do not prove protein expression occurred, then the claims are not adequately described.

It is Applicants' position that if hybridization has occurred, then the gene has already been expressed, not that "gene expression will occur" as stated by the Examiner. While measuring protein expression is one way to determine if a gene is expressed, it is not the only way. Gene expression can also be determined by measuring the presence of mRNA or cDNA. Hence, the specific techniques mentioned by the Examiner are not required to determine gene expression.

Furthermore, protein expression is not required to demonstrate gene expression. A gene can be expressed without yielding a protein. Transcription is the part of gene expression where DNA is copied to messenger RNA. Protein expression does not occur until translation of the mRNA occurs. Contrary to the Examiner's position, Applicants are not measuring hybridization to the gene itself. Rather, Applicants are measuring hybridization to a transcript of the gene. If there is hybridization to a transcript, then transcription has already taken place. Thus, gene expression has already occurred and can be measured by determining hybridization.

These are basic facts of molecular biology. It is Applicants' contention that one of skill in the art at the time the application was filed would have known these facts and understood that

gene expression could be determined in the manner claimed. As such, this rejection should be withdrawn.

With respect to the rejection of claim 55, the Examiner states "there is no primer in claim 51 which would allow the polymerase chain reaction to operate," hence there is not adequate written description to support the claim. *See* Office Action dated January 27, 2004, page 4. In the response filed April 22, 2004, Applicants stated that a primer is a nucleic acid molecule which hybridizes specifically to a transcript, as recited in the claim. In the Advisory Action, however, the Examiner goes on to state,

> "Applicants' have failed to disclose the identity of the nucleic acid sequence which will initiate replication. Applicants' have pointed to claim language and a definition yet still have failed to disclose the nucleic acid identity of the primer."

Applicant directs the Board to page 41, line 16, line 21, line 26 and line 30, where Applicants specifically recite the antisense and sense primers used in the PCR reactions. Furthermore, as previously argued, Applicants describe hundreds of oligonucleotide primers encompassed by SEQ ID NOS: 12, 14-18, 21, 22, 24, 25, 27 and 29. Hence, Applicants believe the Examiner's conclusions with respect to claim 55 are incorrect, and respectfully request that this rejection be withdrawn.

In light of the above, Applicants respectfully assert that the above referenced claims conform with the written description requirement of § 112, first paragraph, because they clearly convey the invention to one skilled in the art at the time the application was filed.

B. The Rejection of Claims 51-58 and 60-61 Under 35 U.S.C. § 112, First Paragraph, for Allegedly Containing New Matter is Improper, and Should be Reversed

The Examiner maintains that claims 51-58 and 60-61 contain new matter because the specification does not contain support for determining gene expression from hybridization. Again, the Examiner seems to confuse gene expression and protein expression, and states in the Advisory Action "[t]here is no support for simply using hybridization to determine protein expression."

This is not what is claimed. Claim 51 et seq. are drawn to determining gene expression, not presence of proteins. Applicants agree with the Examiner that hybridization does not

determine protein expression, but that is not what is claimed. Applicants claim a method for determining expression of a gene, comprising contacting a sample with a nucleic acid molecule which hybridizes specifically to a transcript of the gene, and determining hybridization as a determination of gene expression.

As discussed supra, protein expression is not required to demonstrate gene expression. The first step in gene expression is formation of a transcript. Since Applicants are measuring hybridization to a transcript, this means that gene expression has already occurred. Based on these well known principles of molecular biology, there is adequate support in the specification for determining gene expression from hybridization as claimed.

The Examiner then goes on to state,

> "Because of the low or reduced stringency conditions of the instant claims, the method allows even distantly related genes to be identified; thus the method will include imperfectly matched sequences to be determined."

See Office Action dated January 27, 2004, page 6. As addressed in Applicants' previous response, the recited conditions are not low stringency, but are, in fact, very high stringency.

C. The Rejection of Claims 51-58 and 60-61 Under 35 U.S.C. § 112, Second Paragraph, As Being Incomplete Is Improper and Should be Reversed

The Examiner argues that claims 51-58 and 60-61 are incomplete for omitting essential steps. According to the Examiner, the claims lack steps for determining expression of a gene.

As has been pointed out supra, this rejection is not understood. It appears that the Examiner bases this rejection on the assumption that one cannot determine gene expression from hybridization. The claims, however, require hybridization to a transcript. This de facto means the gene was expressed, which is supported by general principles of molecular biology.

The claims recite a method which first involves "contacting a sample with a nucleic acid molecule ..." and then "determining hybridization as a determination of expression of said gene." There is clearly an affirmative step for determining gene expression involving determining hybridization. Applicants maintain that no steps are missing and that gene expression can be determined by the claimed method. Hence, this rejection should be withdrawn.

D. The Rejection of Claims 51-58 and 60-61 Under 35 U.S.C. § 112, Second Paragraph, As Being Indefinite, Is Improper and Should be Reversed

The Examiner also argues that claims 51-58 and 60-61 are indefinite under 35 U.S.C. §112, second paragraph, for failing to include steps which teach how to determine expression of the gene. This appears to be based on the same reasoning as the rejection in Section C, supra. The Examiner again asserts that the claims lack a positive recitation of method steps that recite how to determine the expression of a gene.

Once again, Applicants' point out that the claims require hybridization to a transcript, which de facto means the gene was expressed.

Further, in both the January 27, 2004 Office Action and the Advisory Action, the Examiner states that the claims lack steps such as "amplification of the hybridized nucleic acid molecule by PCR," and an "immunoprecipitation step." These steps are not required for a nucleic acid hybridization assay.

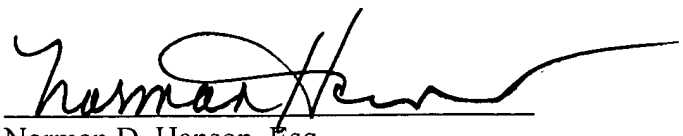
Applicants request withdrawal of this rejection.

IX CONCLUSION

For all of the reasons set forth supra, it is believed that the rejections made under 35 U.S.C. § 112, first paragraph and 35 U.S.C. § 112, second paragraph are improper and should be reversed.

Respectfully submitted,

FULBRIGHT & JAWORSKI, L.L.P.



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LISTING OF CLAIMS ON APPEAL

Claim 51: A method for determining expression of a gene which encodes a human polypeptide that has PI3 kinase activity and a molecular weight of about 110 kiladaltons as determined by SDS-PAGE, comprising contacting a sample with a nucleic acid molecule which hybridizes specifically to a transcript of said gene wherein said transcript is RNA or cDNA, and is selected from the group consisting of (a) the nucleotide sequence set forth in SEQ ID NO: 32; (b) the nucleotide sequence set forth in SEQ ID NO: 35; and (c) the nucleotide sequence which hybridizes to the complement of at least one of (a) and (b), at 1MNaCl, 10xDenhardt's solutions; 50mM Tris-HCL (pH 7.4); 10mM EDTA; 0.1%SDS; 100μg/ml denatured herring sperm DNA at 65^{O}C for 16 hours, followed by a wash of 2XSSC; 0.1%SDS at 42^{O}C, or a wash of 0.5XSSC/0.1% SDS at 50^{O}C, or a wash at 0.1XSSC/0.1%SDS at 65^{O}C, or a wash at 0.1XSSC/0.1% SDS, at 68^{O}C and determining said hybridization as a determination of expression of said gene.

Claim 52: The method of claim 51, wherein said nucleic acid molecule is labeled with ^{32}P.

Claim 53: The method of claim 51, wherein said nucleic acid molecule is an antisense, RNA molecule.

Claim 54: The method of claim 51, wherein said nucleic acid molecule is a DNA molecule.

Claim 55: The method of claim 51, wherein said method comprises polymerase chain reaction.

Claim 56: The method of claim 51, wherein said nucleic acid molecule comprises a nucleotide sequence set forth in SEQ ID NO: 12, 14, 15, 16, 17, 18, 21, 22, 24, 25, 27 or 29.

Claim 57: The method of claim 51, comprising contacting said sample with a pair of oligonucleotide primers, said pair selected from the group consisting of (i) SEQ ID NOS: 12 and 14, (ii) SEQ ID NOS: 15 and 16, (iii) SEQ ID NOS: 17 and 18, (iv)

SEQ ID NOS: 21 and 22, (v) SEQ ID NOS: 24 and 25, and (vi) SEQ ID NOS: 27 and 29.

Claim 58: The method of claim 51, wherein said sample is RNA isolated from a cell sample.

Claim 60: The method of claim 51, wherein said gene encodes a human polypeptide, the amino acid sequence of which is encoded by the nucleotide sequence set forth in SEQ ID NO: 32.

Claim 61: The method of claim 51, wherein said gene encodes a human polypeptide, the amino acid sequence of which is set forth in SEQ ID NO: 37.